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Glucocorticoids Induced Adverse Events in Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis Are Frequent and Often Severe, but Under-Reported: A Systematic Review

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Abstract

Background: Glucocorticoids are cornerstone for treatment of anti-neutrophil cytoplasmic Antibody-Associated Vasculitis (AAV) but their significant dose-dependent toxicity is a major concern in clinical practice. This systematic review aims to determine the frequency and proportion of glucocorticoid-related adverse events in patients with AAV.

Method: A systematic literature search was performed in the Embase, Medline and PubMed databases with limitation on years of publication between January 2000 and December 2020. Full text articles from randomized controlled trials, other interventional and observational studies including data on the study design, population size, drugs administered and adverse events reported were considered for the analyses. Studies focused exclusively on eosinophilic granulomatosis with polyangiitis were excluded. A regression model was run to explore the relationship between mean doses of glucocorticoids, duration and reported adverse events. Furthermore, a correlation matrix was generated to analyse the rate of incidence of adverse events.

Results: A total of 91 articles were reviewed. Most frequently reported serious adverse events included death (12%) and severe infections (9%) while non-serious adverse events included infections (not specified) and leukocytopenia (approximately 14%each). Diabetes was frequently reported according to the Vasculitis Damage Index components. Regression analysis revealed a significant association between duration of glucocorticoid treatment and occurrence of infections and eye disorders (not specified, $p<0.05$). There was no significant association between the mean glucocorticoid dose and occurrence of reported adverse events.

Conclusion: The increasing clinical burden of glucocorticoid-related adverse events in patients with AAV could be reduced by considering advanced therapeutic strategies.

Keywords:

Glucocorticoids • Adverse events • Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis • Steroids

Introduction

Glucocorticoids are routinely used to treat anti-neutrophil cytoplasmic Antibody-Associated Vasculitis (AAV) and other autoimmune disorders [1,2]. It is reported that the European Renal Association-European Dialysis and Transplant Association/European League Against Rheumatism (EULAR) recommendation on treatment regimen has improved the overall survival of patients with AAV; however, the disease and treatment are still associated with significantly increased mortality when compared with the general population [3]. Both short- and long-term uses of glucocorticoids pose a risk of toxicity and potentially life-threatening adverse events [4]. Treatment-associated acute toxicities are believed to cause approximately 60% of deaths. The European Vasculitis Study Group (EUVAS) trials observed high mortality (11%) during the first year of treatment in patients with AAV, and increasing frequency of

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cumulative organ damage, potentially related to glucocorticoids [5-10]. The long-term organ damage includes hypertension, osteoporosis, malignancy and diabetes mellitus [11]. The EULAR recommendations advise monitoring and reporting of glucocorticoid-related adverse events during clinical trials and as a daily practice. In addition, they provide guidance at both the group level and the individual patient level [12]. Although the AE profile of glucocorticoids is well known, under-reporting remains a concern. Therefore, this systematic review was performed to determine the frequency and proportion of adverse events reported in patients with AAV who were exposed to glucocorticoids either alone or in combination with other immunosuppressive therapies [13-20].

Methods

Search strategy

A literature search was performed in Embase, Medline and PubMed databases to identify studies on glucocorticoid-related adverse events in patients with AAV published between January 2000 and December 2020 [21]. The search strategy included a combination of keywords on steroids; disease terms such as AAV, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and Wegener's granulomatosis; and AE-related terms [22].

Study selection

A total of 1869 articles were initially retrieved from the above-mentioned databases. After removing duplicate articles and screening by titles and abstracts, 1545 articles were further excluded [23-30]. The full texts of the remaining 324 articles were reviewed according to the pre-defined inclusion criteria and only 91 articles were included for the systematic review [31].

A comprehensive overview of the systematic literature search is presented in supplementary Figure 1. Studies were considered relevant if they included number of patients enrolled and exposed to steroids, dosage and duration of steroid use, concomitant medications administered and number of patients with adverse events reported after exposure to glucocorticoids. Articles focused on adverse events attributed to other concomitant medications or disease activities were excluded [32].

In addition, patient data on eosinophilic granulomatosis with polyangiitis only were excluded due to its distinct natural history, pathophysiology and treatment paradigm when compared with GPA and MPA. This review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33-36].

The individual EUVAS trials were included for the analysis; however, the concise report from all EUVAS trials by Robson et al [37-40]. Was excluded from the overall analysis as the study determined vasculitis damage rather than adverse events. In addition, sequential publications on the rituximab for anti-neutrophil cytoplasmic AAV (RAVE) trial were excluded to avoid duplication in data entries for the same population data set [41].

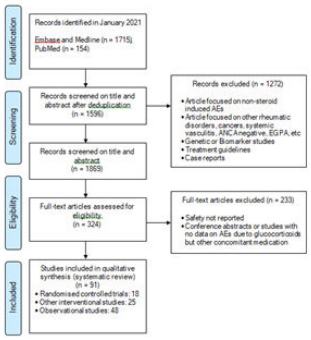

Figure 1: Flow chart for study inclusion: using the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) flow diagram.

Outcome variables

Based on the study design, articles were categorized into three subsets: randomized controlled trials (RCTs), other interventional studies (non-randomized/follow-up/cohort studies where patients received treatment during the course of study) and observational studies (review of medical/hospital charts or records) to assess the proportion of serious and non-serious adverse events attributed to glucocorticoid exposure in patients with AAV [42-45].

Risk of bias assessment

Articles were screened based on the pre-defined eligibility criteria, focusing on the keywords and thoroughly reviewed for data accuracy [46-50]. However, inconsistent data capturing methods and poor documentation was observed across several studies, requiring standardization of the data prior to analyses and lead to challenges to draw any firm conclusion.

Analysis

The glucocorticoid-related adverse events were categorized by system organ class and classified as serious adverse events or non-serious adverse events according to the European Medicines Agency guidelines [51]. Studies reporting adverse events at patient level were considered for the analysis. Data captured on the mean glucocorticoid dosage and duration of exposure was standardized to milligram/day and in weeks [52]. Discrete data was presented as frequencies and percentages in a Microsoft Excel worksheet for further analysis. A regression model was run to explore the relationship between the mean glucocorticoid dose, duration of exposure (in weeks) and reported adverse events [53-60]. Furthermore, a correlation matrix was generated to assess the rate of incidence of the reported adverse events, with $p<0.05$ considered to be statistically significant. The adverse events are presented in a framework according to the components of Vasculitis Damage Index (VDI) [61].

Results

Of the 91 articles included, 18 were RCTs, 25 other interventional [62-70]. And 48 observational studies [70-91]. The characteristics of individual RCTs are presented in supplementary Table 3. The frequency and proportion of serious adverse events and non-serious

adverse events reported from all studies are presented in supplementary Table 4 and Table 5, respectively. Data on adverse events related to glucocorticoid treatment only were considered for the analysis, although there was no evidence on the comorbidities at baseline, in most of the articles.

Serious adverse events

Across the RCTs included in the analysis, 2576 patients were exposed to glucocorticoids and serious adverse events were reported in 1029 patients. The most commonly reported serious adverse events across the RCTs included death (12%), severe (not specified) infections (9%), neutropenia (4%), blood infections (2%), hepatic damage, malignancy, blood disorder affecting platelets, thrombotic disorders, bone fracture, allergy and pulmonary infection (1% each, respectively). Across the other interventional studies included in the analysis, 2204 patients were exposed to glucocorticoids and serious adverse events were reported in 477 patients. The most commonly reported serious adverse events in the interventional studies included bone fracture (8%), severe and pulmonary infections (3% each), death (2%), hearing loss, malignancy and osteonecrosis (1% each, respectively). Across the observational studies included in the analysis, 6048 patients were exposed to glucocorticoids and serious adverse events were reported in 1215 patients. The most commonly reported serious adverse events in the observational studies included death (8%), pulmonary infections (3%), severe infections (2%), blood disorders affecting platelets, thrombotic disorders, sepsis, malignancy and bone fracture (1% each, respectively). Overall, the analysis of all 91 studies in 10,828 patients showed that death (8%) and severe infections (4%) were commonly reported serious adverse events followed by pulmonary infection and bone fracture (2% each, respectively).

Non-serious adverse events

Overall, infections (site and cause unidentified; 14%, 7%, 11%) and leukocytopenia (14%, 0.3%, 4%) were commonly reported non-serious adverse events across the RCTs, interventional and observational studies, respectively. Across the RCTs included in the analysis, 2576 patients were exposed to glucocorticoids and non-serious adverse events were reported in 1512 patients. The most commonly reported non-serious adverse events in the RCTs included leukocytopenia (14%), non-serious infections (not specified; 14%), cardiovascular disorders (7%), gastrointestinal disorders (5%), blood disorder affecting red blood cells and renal disorders (3% each), cardiovascular disorders, vasculitis and diabetes (2% each, respectively), other blood disorder affecting white blood cells, lymphopenia and viral infections (1% each, respectively).Across the other interventional studies included in the analysis, 2204 patients were exposed to glucocorticoids and non-serious adverse events were reported in 621 patients. The most commonly reported non-serious adverse events in the other interventional studies included infections (not specified, 7%), diabetes (3%), hypertension and weight gain (2% each), viral infections, urinary tract infections, osteoporosis, muscle disease, psychiatric disorders, other abnormal pulmonary conditions, chronic sinusitis/radiological damage, acne, breathlessness, cardiovascular, digestive and eye lens disorders (1% each, respectively).

Across the observational studies included in the analysis, 6048 patients were exposed to glucocorticoids and non-serious adverse events were reported in 2347 patients. The most commonly reported non-serious adverse events in the observational studies included infections (not specified, 11%), leukocytopenia (4%), blood disorder affecting red blood cells and skin and mucous membrane disorders (2%), urinary tract infections, diabetes, lymphopenia, viral infections, bacterial infections, gastrointestinal and neuropsychological disorders (1% each, respectively).

Vasculitis damage index

The adverse events reported from RCTs are presented in supplementary Figure 2 according to the VDI components with frequently reported item of damage being diabetes. Although malignancy was also frequently reported, it was considered resultant of exposure to immunosuppressants such as cyclophosphamide (13), azathioprine (16) or mycophenolate (17,18,20). Similarly, the adverse events reported from other interventional and observational studies are presented in supplementary Figure 3 and Figure 4.

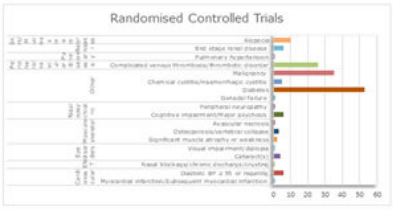

Figure 2: Component bar graph depicting the adverse events reported from randomised controlled trials, presented in the framework according to the components of Vasculitis Damage Index.

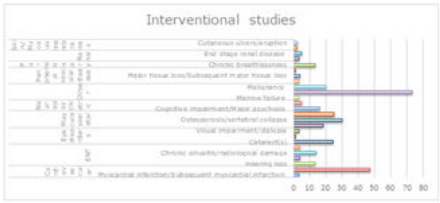

Figure 3: Component bar graph depicting the adverse events reported from other interventional studies, presented in the framework according to the components of the Vasculitis Damage Index.

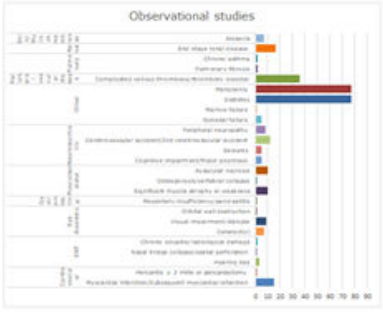

Figure 4: Component bar graph depicting the adverse events reported from observational studies, presented in the framework according to the components of the Vasculitis Damage Index.

Relationship between mean dosage or duration of use of glucocorticoids and reported adverse events

A simple regression model was run at once (without adjusting covariates/factors as there were no confounding factors) for the adverse events with duration as independent variable and the coefficients were captured to analyse the relationship between duration of glucocorticoid exposure and adverse events based on the significance ($p<0.05$) [92]. Regression analysis of the data extracted from the RCTs revealed a significant association between duration of glucocorticoid treatment and occurrence of adverse events including viral infection, fungal infection, peripheral neuropathy, eye disorder (not specified), visual disturbance, pulmonary hypertension, muscle disease, cutaneous eruption, cardiovascular disorder (not specified), myocardial infarction and solid tumours ($p<0.05$; supplementary Figure 5). There was no significant association between the mean glucocorticoid dose and the occurrence of reported adverse events. Regression analysis of the data extracted from other interventional studies did not reveal any significant association between adverse events and the mean glucocorticoid dose or the duration of glucocorticoid exposure [93]. However, regression analysis of the data extracted from observational studies revealed a significant association between the duration of glucocorticoid exposure and the occurrence of diabetes ($p<0.05$; supplementary Figure 6). An overall regression analysis was performed including all three study designs, which revealed a significant association between duration of glucocorticoid exposure and occurrence of adverse events including infections, eye disorders, visual disturbance and pulmonary hypertension ($p<0.05$, supplementary Figure 7). Data on the mean glucocorticoid dose were insufficient across the other interventional and observational studies to analyse the relationship between reported adverse events. The correlation matrices for adverse events from studies on AAV are presented in supplementary Figure 8 and Figure 9.

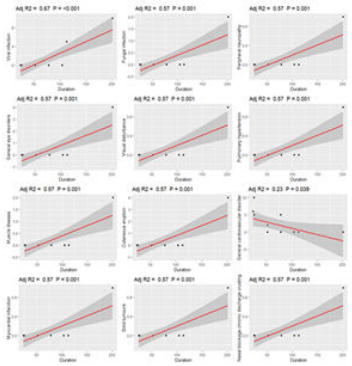

Figure 5: Regression plots depicting the relationship between the duration of glucocorticoids treatment and adverse events reported in randomised controlled trials involving anti-neutrophil cytoplasmic antibody-associated vasculitis patients.

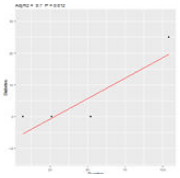

Figure 6: Regression plots depicting the relationship amongst the mean dosage, duration of use of glucocorticoids and adverse events in observational studies.

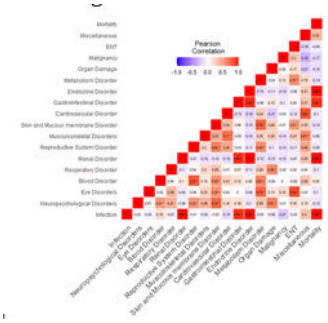

Figure 7: Correlation matrix for adverse events reported from randomised controlled trials involving patients with anti-neutrophil cytoplasmic antibody-associated vasculitis.

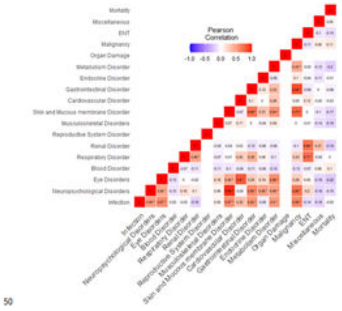

Figure 8: Correlation matrix for adverse events reported from other interventional studies involving patients with anti-neutrophil cytoplasmic antibody-associated vasculitis.

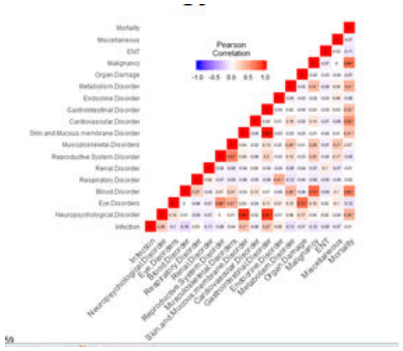

Figure 9: Correlation matrix for adverse events reported from observational studies involving patients with anti-neutrophil cytoplasmic antibody-associated vasculitis.

Discussion

This systematic literature review indicated that patients with AAV who were treated with glucocorticoids alone or in combination with other immunosuppressive therapies reported a wide variety of adverse events involving multiple organ systems, thus leading to a significant increase in mortality and patient burden specifically from infections and blood disorders. This, in turn, increased the healthcare resource burden associated with the management of adverse events. A comprehensive reporting on the glucocorticoid related adverse events and their frequencies were lacking in most of the articles [93-100]. It is also quite possible that some of the adverse events reported in the study such as neutropenia, pulmonary hypertension,

hepatic damage, allergies and organ disorders could have been due to the patient's pre-existing condition or concomitant immunosuppressive therapies namely cyclophosphamide, rituximab, etc. Furthermore, several studies reported no clarity on the relationship between reported adverse events and glucocorticoid treatment. The difference in the frequency and proportion on the occurrence of adverse events among RCTs, other interventional and observational studies could have been due to the varied study designs, inconsistent data capturing methods and poor documentation. Another probable reason could be the under-reporting of adverse events in a few of these studies.

Recently published results from the PEXIVAS trial in patients with severe AAV revealed death from any cause or end stage kidney disease occurred in 92 of 330 (27.9%) patients in the reduced-dose glucocorticoid group and in 83 of 325 (25.5%) patients in the standard-dose glucocorticoid group (absolute risk difference, 2.3 percentage points; 90% CI, −3.4 to 8.0), which met the criterion for noninferiority. Serious infections at 1 year were less common in the reduced-dose glucocorticoid group than in the standard-dose glucocorticoid group (incidence rate ratio, 0.69; 95% CI: 0.52 to 0.93), but other secondary outcomes were similar in the two groups with cardiovascular events being the highly reported at 19% in the reduced glucocorticoid dose group and 16% in standard glucocorticoid dose group [101]. In addition, the interim results from the ADVOCATE trial revealed that serious adverse events reported was generally consistent with previous AAV trials at 45.1% and 42.2% for prednisone and avacopan groups, respectively. Serious infections were 15.2% vs 13.3%, serious hepatic adverse events 3.7% vs 5.4% and serious adverse events of white blood cell count were 4.9% vs 2.4% for prednisone and avacopan, respectively [102-108].

Data analysis from RCTs and observational studies revealed that diabetes, malignancy and thrombosis/thrombotic disorders are the commonly reported items of damage, whereas other interventional studies showed diabetes, hypertension and osteoporosis as the commonly reported items of organ damage. Several RCTs reported malignancy, probably as a resultant of exposure to other concomitant immunosuppressants while some observational studies also reported over 70% of opportunistic infections including pulmonary involvement or lower respiratory tract infections [12, 13].

The extended report of the EUVAS trials by Robson et al. reported proteinuria, glomerular filtration rate of <50 mL/minute and hypertension as the most frequent items of damage in patients with MPA and nasal crusting, hearing loss and peripheral neuropathy in patients with GPA. The high proportion of these disease-related items of damage in the cumulative analysis of the five EUVAS trials reflects high percentage of patients with severe disease in the PEXIVAS trial, which was higher than that in patients with AAV in real life. The EUVAS trial also reported a significant increase in treatment-related items of damage. The percentage of patients reporting malignancy from baseline to the long-term follow-up (12.6%) and the observed cumulative prednisolone dose (>20 mg daily) were significantly associated with increased VDI scores [4]. Furthermore, patients on long-term glucocorticoid use had a threefold higher risk of having ≥5 VDI items of damage (odds ratio: 3.05, 95% confidence interval: 1.76 – 5.30, p<0.001), suggestive of increased morbidity [14].

The clinical risks associated with glucocorticoids at standard dose are well known and have been summarized by the EULAR. The estimated risks, calculated as events per 100 patient-years, were 16 and 3 for osteoporosis, 0 – 1 and 0 – 1 for cardiovascular disease, 1 – 4 and 0 – 2 for peptic ulcer disease and 3 – 28 and 0 – 19 for hypertension amongst glucocorticoid users and glucocorticoid-naïve patients, respectively . The EULAR recommendations on the dosing and benefit-risk profile of glucocorticoids are presented below:

- Before starting treatment with medium- or high-dose glucocorticoids, comorbidities predisposing to adverse events should be considered. Patients with these comorbidities require tight control to manage the benefit-to-risk ratio (Recommendation 6)
- The appropriate starting dose to achieve a therapeutic response should be selected by taking into account the risk of under-treatment (Recommendation 7)
- All patients should be monitored for clinically significant adverse events

The EULAR recommendations advise that physicians should be aware of the risk of adverse events associated with glucocorticoid therapy and periodically monitor and report adverse events at group level and the individual patient level. This could further facilitate in providing the right perspective, early detection and management of the adverse events.

Across studies, there was no clarity in the number of glucocorticoid-related adverse events reported in patients with AAV or if they were monitored regularly for clinically significant adverse events. A higher incidence of reported adverse events was observed in the RCTs in comparison with the other groups, probably due to the nature of the study design, suggesting causal inferences and AE reporting methodology. In contrast, the high number of adverse events reported in observational studies could reflect higher cumulative glucocorticoid dosage in real-world studies. New instruments developed to systematically assess glucocorticoid-related damage, such as Glucocorticoid Toxicity Index [and steroid patient-reported outcome measure (steroid-PROM). Were probably not available during the time of trial designing. Furthermore, there was no clarity on the dosage and duration of glucocorticoid exposure in several studies. Therefore, data ambiguity on the starting dose and tapering schedules were used to maximize the clinical benefit, avoiding under-treatment and minimizing the risk of adverse events. Patients need to be regularly monitored for early detection and management of the adverse events.

An attempt was made to quantify the relationship amongst the glucocorticoid dose, duration of their use and risk of adverse events. The mean glucocorticoid dose and the duration of their exposure were significantly associated with the occurrence of certain serious adverse events and non-serious adverse events. There was no causal relationship between the mean glucocorticoid dose and occurrence of adverse events upon data analysis, which could be due to inconsistent and inadequate data capturing methods across the studies. In addition, studies reporting counts of episodes of adverse events without clinical details were not considered for the analysis. Henceforth, there were challenges in drawing a firm conclusion. Furthermore, a meta-analysis was not performed due to inconsistent and inadequate data for treatment and control arm distinctively across the published literatures.

The strengths of this review lie in its systematic character and comprehensiveness in analysing and presenting patient-level data on glucocorticoid-related adverse events reported for two decades to provide a broader picture of glucocorticoid toxicity in patients with AAV. It also highlights the importance of following clinical guidelines in treating patients with AAV with glucocorticoids, recognising and reporting glucocorticoid-related adverse events and assessing their adverse short- and long-term impact on patients.

However, this study has also several limitations. Exclusion of articles with only available abstracts and inadequate data in the articles resulted in an overall smaller sample size. Patient eligibility criteria in most of the articles were not available, thereby lacking accuracy and evidence on the baseline comorbidity data.

Conclusion

The AE profile of glucocorticoid therapy is quite common and well known. However, the extent of glucocorticoid-related adverse events reported across studies on AAV was not consistent and indicated deficiencies in reporting. Therefore, use of specific instruments for the analysis of glucocorticoid-related adverse events, such as Glucocorticoid Toxicity Index and steroid-PROM, is greatly recommended for future clinical trials. This review highlights the guidelines for the management of patients with AAV on glucocorticoid therapy, recognizing the glucocorticoid-related adverse events, assessing their impact on patients, the importance for gathering and reporting relevant clinical data. Furthermore, the findings from this review necessitate the need for advanced therapeutic strategies for controlling AAV and thereby reducing the significant burden of glucocorticoid-related adverse events, overall mortality and morbidity.

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